Don Hank Translations/ 319 Brook Lane, Wrightsville, PA 17368/ Phone: 717-252-9835/ Fax: 717-252-0674/ E-mail: jlaigle@AOL.com

Italian Patent No. 01293655

CHEWING GUM COMPRISING ACTIVE DRUGS WITH DISINFECTANT ACTION ON THE MOUTH AND THROAT [Gomma da masticare comprendente principi attivi con attività disinfettante del cavo orofaringeo]

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PATENT OF INDUSTRIAL INVENTION

No. 01293655

This patent is issued for the invention specified in the following application:

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Assignee: Gum Base Co., S.P.A.
A. Lainate (Milan)

Representative: Marchitelli Mauro
c/o Jacobacci & Perani S.P.A.

Address: Corso Regio Parco 27
10100 Turin

Title: **CHEWING GUM COMPRISING ACTIVE DRUGS WITH DISINFECTANT ACTION ON THE MOUTH AND THROAT**

Inventors: Sozzi, Giuseppe
Del Viscio, Giovanna

Rome, March 8, 1999

Official in Charge:
Giorgio Rromani
[signature illegible]

A. Assignee

1) Name: Gum Base Co., S.P.A.
Residence: A. Lainate, Milan
Code: 00734730153
2) Name:
Residence:

B. APPLICANT'S REPRESENTATIVE AT THE UIBM

Name: Dr. Francesco Serra [illegible] and others Fiscal Code:
Name of law office: Jacobacci & Parani S.P.A.
Street: Corso Regio Parco No. 27 City: Turin cap: 10152 (prov) TO

C. ADDRESSEE: [left blank]

D. TITLE

CHEWING GUM COMPRISING ACTIVE DRUGS WITH DISINFECTANT ACTION ON THE MOUTH AND THROAT

ANTICIPATED ACCESSIBILITY TO THE PUBLIC: Yes • • No • • [unchecked items omitted]

E. INVENTORS NAMED

1) Giuseppe Sozzi
2) Giovanna Del Viscio

[unfilled items omitted]

ATTACHED DOCUMENTATION

Doc. 1) 1 Prov No. of pages: 20 [unmarked items omitted]
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8) Certification of payment, total lire: 365,000 Dr. Francesco Serra obligatory
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FILED BY official APPLYING OFFICIAL
[signature illegible] stamp [signature illegible]

[illegible]
A. APPLICANT(S):

Name: Gum Base Co., S.P.A.
Residence: Lainate, Milan

D. TITLE: **CHEWING GUM COMPRISING ACTIVE DRUGS WITH DISINFECTANT ACTION ON THE MOUTH AND THROAT**

L. ABSTRACT

Chewing gum composition comprising a gum base and an active drug having antibacterial and/or disinfectant activity in the mouth and throat, characterized by the fact that the gum base comprises, per 100 parts of gum base.

– from 2 to 20% by weight of natural or synthetic elastomers;
– from 25 to 60% by weight of resins acting as plasticizers for the elastomer;
– from 2 to 15% by weight of microcrystalline waxes;
– from 0 to 20% hydrogenated vegetable oils;
– from 1 to 15% by weight of emulsifiers and
– from 0 to 35% by weight of any bulking agents, vehicles or glidants.

Description of the industrial invention entitled:
CHEWING GUM COMPRISING ACTIVE DRUGS WITH DISINFECTANT ACTION ON THE MOUTH AND THROAT

Assignee: Gum Base Co., S.p.A., Italian nationality, Via Nerviano 25, Lainate (Milan)

Inventors named: Giuseppe Sozze, Giovanna Del Viscio

Filed: July 29, 1997

The present invention relates to a chewing gum comprising a gum base and an active drug having antibacterial and/or disinfectant activity in the mouth and throat.

It is known to use chewing gum as a pharmaceutical form and vehicle for administration of therapeutically active agents; for example, FR-A-2320083 and US 1,396,641 describe chewing gums that comprise a disinfectant agent.

A problem relating to the administration of disinfectant agents of the mouth and throat through the use of chewing gum lies in the existence of a gradual and increasingly complete release of the active agent within the consumer's normal chewing times, typically on the order of ca 15-30 min. A too-rapid release of the active drug practically cancels the advantages of this form of administration, which reside essentially in the persistence of the drug in the mouth and throat for an extended period of time; on the other hand, a sustained or too-slow release is not desirable because it would result in only partial or no administration of the drug within the usual chewing time.

It is also particularly desirable for the release pattern of the therapeutically active drug to be gradual and similar to the release pattern of the flavoring agents contained in the chewing gum so that the drug can be released in therapeutically efficacious doses within a time period corresponding to the period in which the gum maintains a pleasant flavor and aroma. This requirement is particularly important with regard to drugs that have a pleasant or bitter taste, because the release of the flavoring and sweetening agents is useful in masking the unpleasant organoleptic sensation produced by the drug.

The release problem is also particularly relevant in the case of drugs having a molecule with lipophilic characteristics that tend to be retained in the matrix of the gum base.

The above-described problems pertaining to release are not solved by the prior-art patents listed above. French Patent FR-A-2320083 indicates that the active agent is released only after 15 minutes. In an attempt to overcome these drawbacks, the patent EP-B-0 399 479 proposes a chewing gum containing disinfectants of the mouth and/or throat, and specifically, cetylpyridinium chloride, benzalkonium chloride and dequalinium chloride, wherein the gum base used consists of latex and the usual additives in the form of small granules with sizes ranging from 0.2 to 1 mm, mixed with a lipoid substance; in the preparation process the gum base is ground to the form of particles and combined with particles of an additive coated with a fat or wax and the mixture of gum base and particles with the disinfectant agent added is formed into tablets.

The main disadvantage regarding the above-described type of formulation is that the chewing gum contains the gum base in granular form, which is not well accepted by the consumer because the organoleptic sensation produced by the presence of a granulate is not pleasant and is substantially different from that produced by a typical chewing gum. Indeed, it is only following more or less prolonged chewing that the gum can be homogenized into a plastic mass.

One purpose of the present invention is to provide a chewing gum composition that has the optimum drug release characteristics described above.

Another purpose of the invention is to provide a chewing gum composition that is well accepted and pleasant to the consumer and has organoleptic properties quite similar to those of a conventional chewing gum.

In view of these goals, the purpose of the invention is a chewing gum comprising a gum base and an active drug having antibacterial and/or disinfectant activity on the throat and mouth, characterized by the fact that the gum base comprises, per 100 parts of gum base:

- 2-20% by weight of natural or synthetic elastomers,
- from 25 to 60% by weight of resins acting as plasticizers for the elastomers;
- from 2 to 15% by weight of microcrystalline waxes;
- from 0 to 20% hydrogenated vegetable oils;
- from 1 to 15% by weight of emulsifiers;
- from 0 to 35% by weight of any bulking agents, vehicles or glidants.

Preferred as elastomers are synthetic elastomers, particularly polyisobutylene, isobutylene-isoprene copolymer and butadiene-styrene copolymer; however, natural gums conventional present in chewing gum, which are not preferred because they are capable of increasing stickiness of the gum, can also be used.

The resins acting as plasticizers for the elastomer include polyterpene resins, derivatives of alpha-pinene, β-pinene and/or d-limonene, so-called ester gums or rosin esters such as esters of partially hydrogenated rosin glycerols, esters of polymerized rosin glycerol, esters of rosin pentaerythritol, partially hydrogenated rosin methyl esters and also polyvinyl acetate of high or low molecular weight.

Combinations of polyterpene resins in quantities of 12-60%, partially hydrogenated rosin esters in quantities of 4-38% and polyvinyl acetate in quantities of 25-70% as against total resin weight are preferred. The polyvinyl acetate used can have a weight average molecular weight in the range of 12,000-75,000 and preferably 12,000-50,000.

The microcrystalline waxes are preferably used in quantities of 2-15% by weight in combination with hydrogenated vegetable oils in quantities of 2-20% by weight. The hydrogenated vegetable oils are preferably palm, soya and cottonseed oils. To improve the release of active drug, it is preferable that the weight ratio between hydrogenated vegetable oils and microcrystalline waxes in the chewing gum base be in the range of 1.1-2.1.

The emulsifiers, generally used in the range of 1-50% by weight, preferably include lecithin, particularly oleate-free soybean lecithin, glycerol monostearate, acetylated monoglycerides and triacetin.

The quantity of fillers in the gum base can vary within wide limits, from 0 to 35% by weight. Used as fillers, in particular, are talc, calcium and magnesium carbonate, silicates, titanium dioxide, aluminum[1], clay, calcium phosphates and combinations thereof.

The inventive chewing gum can be in the form of regular chewing gum or bubble gum. Chewing gums comprise all conventional forms such as coated gums (dragees), stick gum, cushions and the like.

It is intended that the composition of the gum base can be varied within the wide ranges specified depending on whether the finished product is of the regular chewing or bubble gum type.

Thus, as known to those skilled in the art, particularly the quantities of resins acting as plasticizers for the elastomer will be varied in the case of bubble gum base; in this case, for example, concentrations of 15-30% polyvinyl acetate in combination with 5-15% polyterpene resin and 1-15% ester gums are preferred.

The gum base for either chewing gum or bubble gum is prepared by conventional processes, typically with the use of double-Z mixers (sigma blade mixers) at a temperature typically in the range of 60-150• C, preferably in the range of 80-120• C. The molten mass is then unloaded from the mixer and is then extruded or cast in the desired form and allowed to solidify by cooling.

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[1] Apparently a typographic error. Later context mentions an aluminum compound–Tr.

In the inventive chewing gum, the gum base typically constitutes from 15 to 50% by weight of the total composition.

The final formulation of the chewing gum comprises the active drug, and the conventional water-soluble components comprising sweeteners, flavors and possibly subsequent emulsifiers or stabilizers, uniformly dispersed in the gum base.

The therapeutically active drug having disinfectant and/or antibacterial activity in the mouth and throat is preferably selected from the group consisting of dequalinium chloride, dequalinium acetate, chlorhexidine, domiphen, benzalkonium saccharinate, dodequinium bromide, acetylpyridinium chloride, chlorothymol, phenyl salicylate, benzocaine, hexetidine, benzoxonium chloride, tribenzonium iodide, benzidamine, aluminum lactate and mixtures thereof. Particularly preferred as the active drug is dequalinium, preferably in the form of dequalinium acetate or chloride, available in highly pure form and quality through Laboratori MAG S.p.A.

The concentration of the active drug is generally in the range of 0.04-0.12% by weight as against the weight of the gum base.

The sweeteners include sugar-based sweeteners, non-sugar sweeteners and intense sweeteners. Sugar-based sweeteners include sucrose, dextrose, maltose, fructose, glucose; non-sugar sweeteners are preferably selected from among sorbitol, mannitol, xylitol, maltitol and isomaltitol. The intense sweeteners can include aspartame, acesulfame, saccharin, thaumatin, monellin and dihydrochalcones.

In a special variant of the invention, the gum base composition comprises neohesperidine dihydrochalcone in concentrations on the order of ca 0.005-2% by weight as against the weight of the chewing gum. Preferably, a complex of neohesperidine dyhdrochalcone with a cyclic oligosaccharide, particularly β-cyclodextrin or gamma-cyclodextrin, is used. This complex is prepared ahead of time and is dispersed in the gum base during preparation of the chewing gum composition, together with the other ingredients listed above. The use of this complex is particularly preferred when the active drug consists of dequalinium chloride or acetate. In fact, the presence of this sweetener in complexed form, particularly with β-cyclodextrin, is found to provide for slow release of the sweetener over a gum chewing time of ca 15-20 minutes, and the sweetener is released in parallel with the release of the dequalinium, thereby masking the extremely bitter taste. This affords a product that is acceptable and agreeable to the consumer.

The inventive chewing gum composition comprises conventional flavors typically in amounts of 0.1-10% by weight, preferably 0.5-3% b weight. The flavors can be selected in view of the organoleptic characteristics of the active drug so as to mask any unpleasant or bitter taste. Preferred are peppermint or spearmint flavors, wintergreen oil and fruit essences.

The chewing gum is prepared by mixing the ingredients, preferably with the gum base prepared before it is introduced into the mixer or directly in the mixer. The sweeteners and subsequently, the flavors and the therapeutically active drug are added to the gum base in the mixer.

After mixing, the mass is discharged and subsequently processed into the desired form, for example, by rolling into sheets and cutting to obtain slabs or by extrusion.

The following examples illustrate gum base formulations that can be used within the scope of the invention for chewing gum (Examples 1-5) and bubble gum (Examples 6-8).

Examples 9-13 refer to formulations of chewing gum as a finished product which contains the gum bases according to Examples 1-5.

The chewing gum formulation of Example 9, including the gum base of Example 1, was tested to determine the transfer of active drug, in this case, dequalinium chloride. For this purpose, sticks of chewing gum weighing 2.5 g and containing 0.5 mg each of dequalinium chloride were used.

The following procedure was used for unchewed sticks and sticks chewed for times of 2, 10, 20, 40 and 60 minutes, respectively, containing dequalinium chloride in the rated concentration of 0.6 mg.

The chewing tests were conducted by a panel of volunteer gum chewers consisting of 10 persons. After chewing for times ranging from 5 to 60 minutes, each stick of chewing gum was weighed, frozen

with liquid nitrogen and ground in a mortar with dry-ice cooling. The powder thus obtained was collected in a test tube and 10 mL of methanol was added, after which the samples were stirred in a vortex for 15 min and centrifuged at 3000 rpm for 30 min at 35• €. The supernatant thus obtained was transferred to a 1 mL test tube and centrifuged at 13,000 rpm for 30 min. The analysis of the dequalinium chloride content before and after chewing was conducted with a Beckman 112 HPLC equipped with a Kontron 430 detector with a variable λ and an Ultrasphere ODS column, 5 μ, 4.6 mm × 25 cm. Elution was performed with a solution of 1.92 g of pentanesulfonic acid in 1 liter of water to which tetrahydrofuran was added in a proportion of 750:250; the solution was then adjusted to pH 2.5 with phosphoric acid, filtered under vacuum using a standard filter and degassed for 15 min.

The dequalinium chloride content in the extract was determined using a rectilinear calibration curve based on standard samples having a known dequalinium content. The results obtained for chewing gum chewed for 20 minutes showed a residual dequalinium chloride content in the range of 35-45% by weight as against the starting value.

After 60 minutes of chewing, the residual content was on the order of 30% by weight.

The tests conducted on samples subjected to brief chewing times (5 minutes) also revealed immediate release of a fraction of about 20-30% of the starting content.

Examples 1-5: Gum Base for Chewing Gum (% by weight)

	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5
Isobutylene-isoprene copolymer	4.5	3.6	4.5	4.0	2.7
Polyisobutylene elastomer	8.2	9.1	9.7	6.3	10.1
Partially hydrogenated rosin esters	4.8	5.2	2.2	3.4	6.2
Terpene esters	23.2	24.4	29.9	21.1	21.7
Polyvinyl acetate	16.2	15.8	20.7	14.1	10.3
Hydrogenated vegetable oil	13.0	7.8	11.5	13.5	9.2
Microcrystalline wax	7.0	6.5	6.5	6.7	8.3
Glycerol monostearate	6.3	9.1	8.2	8.0	7.3
Calcium carbonate	16.0	–	–	–	23.2
Talc	–	17.2	4.6	22.0	–
Lecithin	0.8	1.3	2.2	0.9	1.0

Examples 6-8: Gum Base for Bubble Gum (% by weight)

	Ex. 6	Ex. 7	Ex. 8
Isobutylene-isoprene copolymer	–	2.2	4.4
Polyisobutylene elastomer	2.1	10.7	3.6
Partially hydrogenated rosin esters	4.6	14.6	7.5
Terpene esters	8.2	5.0	12.0
Polyvinyl acetate	24.8	18.7	29.8
Hydrogenated vegetable oil	5.2	–	2.2
Microcrystalline wax	10.1	5.9	8.1
Glycerol monostearate	10.4	7.0	6.2
Calcium carbonate	–	–	21.2
Talc	23.1	33.1	–
Lecithin	0.5	0.8	1.4
Glyceryl triacetate	1.0	2.0	3.6

Examples 9-13: Formulation of Chewing Gum as Finished Product (% by weight)

	Ex. 9	Ex. 10	Ex. 11	Ex. 12	Ex. 13
Gum base	22.0	21.5	32.0	30.0	32.0
Glucose 45 Bé	19.0	–	–	–	–
Glucose 43 Bé	–	18.0	–	–	–
Sorbitol 70%	2.0	–	9.0	10.0	–
Lycasin 85%	–	–	–	–	12.0
Sugar	54.08	58.63	–	–	–
Powdered sorbitol	–	–	39.23	33.95	33.66
Mannitol	–	–	3.0	1.5	4.0
Xylitol	–	–	12.0	14.0	15.0
Isomalt	–	–	–	7.0	–
Sweetener**	0.1	0.1	0.15	0.13	0.12
Flavoring	0.8	0.75	1.6	1.4	1.7
Dequalinium*	0.02	0.02	0.02	0.02	0.02
Glycerin	2.0	1.0	3.0	2.0	1.5

* chloride or acetate
** complex of β-cyclodextrin and neohesperidin dihydrochalcone

Claims

1. Chewing gum composition comprising a gum base and active drug having antibacterial and/or disinfectant activity on the mouth and throat, characterized by the fact that the gum base comprises, per 100 parts of gum base:
– from 2 to 20% by weight of natural or synthetic elastomers
– from 25 to 60% by weight of resins acting as plasticizers for the elastomer;
– from 2 to 15% by weight of microcrystalline waxes;
– from 0 to 20% hydrogenated vegetable oils;
– from 1 to 15% by weight of emulsifiers and
– from 0 to 35% by weight of any bulking agents, vehicles or glidants.

2. Composition according to Claim 1, characterized by the fact that the elastomers are chosen from the group consisting of polyisobutylene, isobutylene-isoprene copolymer and butadiene-styrene copolymer.

3. Composition according to Claim 1 or 2, characterized by the fact that the resins acting as plasticizers for the elastomer are selected from the group consisting of polyterpene resins, rosin resins and polyvinyl acetate and mixtures thereof.

4. Composition according to Claim 3, characterized by the fact that the component made up of resins that plasticize the elastomer comprises:
– from 12 to 60% by weight of polyterpene resins

– from 4 to 38% by weight of partially hydrogenated rosin esters and

– from 25 to 70% polyvinyl acetate.

5. Composition according to any of Claims 1 through 4, comprising 2-15% by weight of microcrystalline waxes in combination with 2-20% by weight of hydrogenated vegetable oils.

6. Composition according to Claim 5, wherein the weight ratio between hydrogenated vegetable oils and microcrystalline waxes in the gum base ranges from 1.1 to 2.1.

7. Composition according to any of the above claims wherein the emulsifiers are selected from the group consisting of de-oleated soybean lecithin, glycerol monostearate, acetylated monoglycerides and triacetin.

8. Composition according to any of the above claims wherein the active therapeutic drug is selected from the group consisting of dequalinium chloride, dequalinium acetate, chlorhexidine, domiphen, benzalkonium saccharinate, dodequinium bromide, acetylpyridinium chloride, chlorothymol, phenyl salicylate, benzocaine, hexetidine, benzoxonium chloride, tribenzonium iodide, benzidamine, aluminum lactate and their mixtures.

9. Composition according to Claim 8, wherein the active drug is either dequalinium acetate or dequalinium chloride.

10. Composition according to any of the above claims wherein the active drug is contained in quantities of 0.04-0.12% by weight as against the weight of the gum base.

11. Composition according to any of the above claims, comprising neohesperidin dihydrochalcone as the sweetener.

12. Composition according to Claim 11, comprising a complex of neohesperidin dihydrochalcone with a cyclic oligosaccharide.

13. Composition according to Claim 12, wherein the cyclic oligosaccharide is β- or γ-cyclodextrin.